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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROGERS, JAMES WILLIAM	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
09/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,045	CHAU ET AL.	
	Examiner	Art Unit	
	James W. Rogers, Ph.D.	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-23,29,33,39 and 43-56* is/are pending in the application.

4a) Of the above claim(s) *24-28,30-32,34-38 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) *15,16,19,20,23,45,46 and 53* is/are allowed.

6)☒ Claim(s) *1-6,9-14,17,18,21,22,29,33,39,43,44,47-52 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any objection/rejection from the previous office action filed 03/21/2007 not addressed in the office action below has been withdrawn.

Allowable Subject Matter

Claims 15,16,19-20,23,45,46 and 53 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 1st and 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Response to Arguments

Rejection under 35 U.S.C. 112, 1st paragraph Enablement and Written Description.

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

Note: the examiner retracts his statement that claims 1-2 and 12-13 are reach through claims, they are not reach through claims.

Applicants assert that the examiner has presented only one factor in determining whether one of ordinary skill could make and use the claimed composition. Applicants assert that based on the amount of guidance provided in the specification, quantity of experimentation necessary, presence of working examples and breadth of the claims one of ordinary skill in the art would be able to make and use the claimed composition without undue experimentation.

1. **Breadth of claims**: Applicants assert the enzymes which cleave the oligopeptide recognition segment are well known.

The relevance of this assertion is unclear, the enablement rejection is over the oligopeptide recognition segment (linker), it would be undue experimentation to find what particular peptide segments are cleavable by the specific digestive enzymes recited within the claims.

2. **State of Prior Art**: Applicants assert the examiner has only used part of the definition of the term "digestive enzyme" and the claims are restricted to serine proteases and matrix metalloproteinases which show specificity.

   The relevance of this assertion is unclear and confusing. Once again the examiner applied the **enablement rejection over the oligopeptide linker units not the digestive enzyme that cleaves them**. As stated in the previous office action the state of the art for peptide linkers cleavable by the specific digestive enzymes claimed is very low; this is verified by applicants own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences". Thus the skilled artisan must carefully select a peptide that is cleavable by a select digestive enzyme, a select digestive enzyme will not cleave any peptide sequence because the digestive enzyme is very selective.

3. **The amount of direction or guidance presented in the application and quantity of experimentation:** Applicants assert that one skilled in the art would have no difficulty in determining what sequences are cleaved by a variety of different enzymes that could cleave a target linker. Applicants state that there are

many methods described in the specification to determine the cleavage motif of a target enzyme when it is not yet known.

The above description for how to determine what sequence is cleavable by an enzyme is considered undue experimentation. Applicants are essentially stating that one of ordinary skill could perform an assay to determine whether a particular linker is suitable. Performing assays to find new peptide linkers that are cleavable by applicants claimed digestive enzymes is undue experimentation and also reads on peptide linkers yet to be sequenced. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

4. **Presence of working examples**: Applicants assert that there are working examples within Appendix A and the references cited.

As detailed in the previous office action applicants are enabled for the linkers described in appendix A with the following oligopeptide sequences IPVGLIG, IPVGLI, IPVGL and IPVG.

Written Description

Applicants assert that there is adequate written description because the enzymes are well characterized and there is no requirement to provide detailed information on materials that are publicly known and available to the public.

The relevance of this assertion is unclear, as stated above the examiner applied the 112 1st rejection over the oligopeptide linkers not the enzymes that cleave them. While there is written support for the specific oligopeptide linkers IPVGLIG, IPVGLI, IPVGL and IPVG cleavable by MMP-2 there is no written support for oligopeptide linkers that are cleavable by serine proteases or matrix metalloproteases. Note that the species MMP-2 does not define the genus of metalloproteases recited in claims 1 and 12-13.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Within claim 4 the recitation that the size of the polymeric carrier is larger than the renal excretion limit is indefinite as cited in the previous action filed 03/21/2007.

Response to Arguments

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

Applicants assert that they have defined the phrase adequately because applicants are their own lexicographers.

The relevance of this assertion is unclear. While it is known in the art as shown by applicants that microparticles which are to large exhibit marked inhibition on renal

clearance, however it is not clear what size would preclude renal clearance because the physical size that would preclude clearance is not claimed nor adequately described within the specification. One of ordinary skill in the art when reviewing applicant's claims could not ascertain what polymers are excluded by the functional limitation "renal excretion limit" without a recitation of an actual physical limitation such as the size of the polymer. It is strongly suggested by the examiner that applicants limit claim 4 by an actual size limitation for the polymeric carrier supported within the specification because a recitation of renal excretion limit is indefinite with respect to the size of the carrier that would be excluded.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6,9-13,17,21,29,33,39,43,47-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Copland et al. (WO 01/68145 A2), for the reasons set forth in the office action dated 03/21/2007.

Response to Arguments

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

Applicants assert that Copland does not suggest compositions containing a polymeric carrier. To support this assertion applicants show a diagram of the PEG amino capping group with two ethanol moieties and states this is not a polymer.

This assertion is misleading and wrong. The formula within Copeland is the following:

$H_3CO-(CH_2CH_2O)_t-CH_2C(=O)-$, **wherein t is 1 to 10**. Polymers are large molecules comprised of repeating monomeric units, clearly if t=2-10 the above structure contains a repeat monomeric unit, thus meeting applicants claim to a polymer carrier. Also since the enzyme selective peptide sequences are sequences in a larger polypeptide the rest of the peptide not cleaved by the digestive enzyme can be considered as a polymer carrier, since peptides are poly amino acids.

Applicants assert Copeland does not suggest polymeric carriers having a size larger than the renal excretion limit.

As described above this claim is indefinite as to what sizes would be excluded by this limitation. Since the limitation is unclear the burden is shifted to applicants to show that the polymeric carriers of Copeland are not larger than the renal excretion limit.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6,9-14,17,18,21,22,29,33,39, 43,44,47-52 and 54-56 are rejected under 35 U.S.C. 102(b) as being unpatentable by Duncan et al. (WO 98/56425, cited in last office action) in view of Copeland et al. (WO 01/68145 A2), for the reasons set forth in the office action dated 03/21/2007.

Response to Arguments

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

Applicants asserts that Duncan does not disclose or suggest a conjugate containing a polymeric carrier, a drug molecule and a linker that includes a 1st and 2nd end. Applicants also assert that Copland does not disclose or suggest a composition containing a polymeric carrier as required by the claims.

The relevance of these assertions is unclear. Duncan clearly discloses that the prodrugs are activatable by digestive enzymes (injected before or after in the tissue, thus they are over-expressed in that area), in which the drug (including doxorubicin and methotrexate) is connected covalently to a linker (including peptides), which is further connected to a hydrophilic polymer (including dextran). Copeland as detailed above does describe a polymeric carrier (dextran) as required by applicants claims.

Applicants further assert that the claimed compositions and methods do not require sequential administration of two compositions as required by Duncan.

The relevance of this assertion is unclear. Applicants claims as currently amended do not preclude a sequential administration of a digestive enzyme. Applicants claims are drawn to a composition (Claim 1), a method of preparing a conjugate (claim

12) and a method of targeting a drug to a tissue in a patient (Claim 13). The only claim in which applicant's assertions are relevant is claim 13, but the recitation "digestive enzyme is overexpressed in the extracellular space of the tissue" dos not preclude enzymes that are administered to the tissue site to achieve overexpression. Clearly if an enzyme is delivered to a site (tissue) it will be overexpressed, applicants claimed invention does not preclude administrating an enzyme to the site to achieve overexpression.

Applicants lastly assert that one of ordinary skill would not be motivated to combine the two-component compositions of Duncan with the non-polymeric compositions of Copeland to arrive at the claimed conjugates.

The relevance of these assertions is unclear. As recited above Copeland does read on applicant's claimed polymeric carriers. The two references are clearly combinable because they are closely related in that the drug conjugates are structurally similar in that each contains a drug, peptide linker which can further be linked to a polymer end unit. The motivation for combining them would be to produce a drug conjugate with the advantage of linkers that have MMP-2 cleavable peptides as described within Copland, thus the prodrug would be targeted to tissue where MMp-2 is over expressed such as carcinomas tissue, thus the compounds are inactive or significantly less active upon administration to non-diseased tissue, thus lowering the toxicity.

Conclusion

No claims are allowed at this time.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James W. Rogers, Ph.D. whose telephone number is (571) 272-7838. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on (571) 271-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER